REMARKS

Applicants have carefully studied the Office Action mailed on December 20, 2006. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

March 21, 2006 telephonic interview with Examiner Zachary C. Howard and Supervisory Examiner Anthony Caputa

Applicants gratefully acknowledge the courtesy shown by Examiner Zachary C. Howard and Supervisory Examiner Anthony Caputa during a telephonic interview with applicants' representative, Lisa D. Tyner, on Tuesday, March 21, 2006.

During the interview, the applicants' representative discussed the outstanding rejections.

Status of the claims

Claims 30-72 have been canceled without prejudice. New claims 73-79 have been added. Support for new claim 73 is found in the specification at, for example, p. 32, ll. 19-23, p. 34, ll. 19-21, Example 2 on p. 39, ll. 2-14, Example 8 on pp. 46-48, ll. 20-17, Example 9 on p. 48, ll. 19-32, Example 10 on p. 49-50, ll. 1-25, Example 13 on pp. 54-57, ll. 27-17 and Figure 26 and the original claims as filed. Support for new claim 74 can be found in the specification at p. 3, ll. 17-18, p. 17, ll. 21-22. Support for new claim 75 can be found in the specification at p. 4, ll. 9-12, p. 7, ll. 9-13, p. 8, ll. 10-14, p. 17, ll. 24-27, p. 26, ll. 4-8, and pp. 27-28, ll. 32-2. Support for new claim 76 can be found in the specification, p. 33, ll. 29-31, p. 34, ll. 1-2 and Example 14 on pp. 57-58, ll. 22-4. Support for new claim 77 can be found in the specification at p. 32, ll. 9-11 and ll. 20-21. Support for new claims 78 and 79 can be found in the specification at p. 32, ll. 9-11 and ll. 31-33, p. 34, ll. 19-21, p. 39, ll. 5-8, and p. 40, ll. 4-6. No new matter has been added. Claims 73-79 are pending and at issue.

Objection to claims 21, 22, 24, 30-37, 39-49, 52, 53 and 55-58

Claims 21, 22, 24, 30-37, 39-49, 52, 53 and 55-58 have been objected to as encompassing non-elected species. The elected species was the binding motif of ^{598}HSRSLP^{603} and the cellular activity of cell survival.

Claims 21, 22, 24, 30-37, 39-49, 52, 53 and 55-58 have been canceled without prejudice. Claims 73-79 recite a method of regulating hematopoietic cell survival by targeting a mutation to a binding motif capable of binding a cytoplasmic protein of a GM-CSF/IL-3/IL-5 receptor of a hematopoietic cell. The receptor has a beta-chain having an amino acid sequence according to SEQ ID NO: 1 and the binding motif has the amino acid sequence ^{598}HSRSLP^{603}. At least one of the residues of the binding motif is capable of being mutated. Accordingly, applicants submit that the claims read on the elected species. Withdrawal of this objection is respectfully requested.

Enablement rejection

Claims 21, 22, 24, 30-37, 39-50 and 52-58 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, the specification, while enabling for an *in vitro* method of stimulating hematopoietic cell survival by regulating phosphorylation of a $ß_c$ chain, does not reasonably provide enablement for a method of activating or regulating cellular activities by regulating phosphorylation of a binding motif of a receptor or a functional equivalent or analogue thereof (*see* Office Action dated December 20, 2005, paragraph spanning pp. 4-5). Additionally, the Examiner contends that claim 42 lacks enablement for functional equivalents and analogues of the specified amino acid sequence.

Claims 21, 22, 24, 30-37, 39-50 and 52-58 have been canceled without prejudice. Applicants respectfully traverse this rejection with respect to the new claims, all of which depend from new claim 73.

Although applicants respectfully disagree with the Examiner's contentions, in order to expedite prosecution, the claims have been amended to recite a specific cell type (hematopoietic - e.g., CTL-EN cells), receptor type (GM-CSF/IL-3/IL-5) and cellular activity type (cell survival).

Applicants have discovered that mutation of the cytoplasmic protein binding motif ^{598}HSRSLP^{603} affects its capability to be phosphorylated and can regulate cell survival. Thus, applicants have shed light on the "poorly understood" "link between the triggering molecule and receptor and actions such as cell survival" and, *for the first time*, have disclosed the importance of the binding motif ^{598}HSRSLP^{603} to cell survival (specification, p. 1, ll. 18-23).

Hematopoietic cell survival is a downstream result of interactions between extracellular and cytoplasmic proteins and a GM-CSF/IL-3/IL-5 receptor (specification, p. 32, ll. 9-17). As discussed in the specification, extracellular proteins, upon binding to the receptor, cause phosphorylation of the binding motif (specification, p. 32, ll. 16-19, p. 18, ll. 28-32; *see also* p. 4, ll. 14-18, p. 29, ll. 14-20). The phosphorylated binding motif attracts cytoplasmic proteins that, in turn, give rise to a series of cascading events resulting in cell survival (*Id.*; Example 7 (particularly, p. 45, ll. 2-3) and p. 32, ll. 19-20).

Cell survival, as it is linked to phosphorylation, may be regulated by any means which results in inhibition or activation of the phosphorylation of the binding motif (specification, pp. 31-32, ll. 22-7). That is,

> [r]egulation of cell survival may include enhancing or reducing cell survival or even causing cell death. This may be achieved by enhancing or inhibiting any of the steps described above. For instance enhancing phosphorylation of the binding motif may enhance survival. Alternatively, inhibiting phosphorylation may inhibit cell survival (specification, p. 32, ll. 19-23).

While inhibition of phosphorylation leads to apoptosis and cell death, activation of phosphorylation leads to cell survival (specification, p. 32, ll. 3-7, Figures 17, 18, 24 and 26).

Regulation of hematopoietic cell survival by mutation of a binding motif of a GM-CSF/IL-3/IL-5 receptor is shown in Example 8 on pages 46-48 of the specification. Specifically, experiments using CTL-EN cells (Cytotoxic T-Lymphocyte-Ecotrophic retroviral receptor Neomycin cells), a type of hematopoietic cell, expressing either the wild type ^{598}HSRSLP^{603} or a mutant receptor (EFAAAA) were performed under low serum conditions (0.1% FCS) in the presence of IL-3 to test for cell survival. Those cells expressing ^{598}HSRSLP^{603} remained "greater

than 90% viable for up to 3-4 days" (specification, pp. 47, ll. 6-10). In contrast, CTL-EN cells expressing the mutant receptor in the presence of IL-3 remained only 7% viable after 4 days (*id.*). This indicates that the ability to phosphorylate and attract 14-3-3 (a cytoplasmic protein) "is important for maintaining cellular viability" (specification, p. 47, ll. 31-32). Thus, Example 8 demonstrates that hematopoietic cell survival can be regulated by mutation of the GM-CSF/IL-3/IL-5 receptor.

Additionally, Examples 4 and 10 demonstrate the importance of phosphorylation of the ^{598}HSRSLP^{603} binding motif for attracting cytoplasmic proteins such as 14-3-3. Example 4 shows that the mutated receptor down-regulates the phosphorylation and binding of cytoplasmic proteins to the binding motif *in vivo* (specification, Example 4, pp. 40-41). Example 4 also demonstrates that the serine residue at position 601 is phosphorylated *in vivo* in response to binding of an extracellular protein, GM-CSF, to the receptor. In Example 10, the phosphorylation of the residue at position 601 in cells expressing either the wild type or mutant receptors was measured in after the cells were stimulated with IL-3, an extracellular protein (specification, Example 10, pp. 49-50). It was found that phosphorylation of the serine residue at position 601 in cells expressing the wild type receptor was up-regulated in response to IL-3 whereas cells expressing the mutant receptor did not respond to stimulation with IL-3. As shown by these examples, mutation of one or more of the residues of ^{598}HSRSLP^{603} can be used to regulate phosphorylation of the receptor and, hence, the cell's survival.

For the foregoing reasons, the pending claims are enabled and applicants respectfully request withdrawal of this rejection.

Written description rejection

Claims 21, 22, 24, 30-37, 39-50 and 52-58 under 35 U.S.C. § 112, first paragraph, have been rejected for lack of written description.

Claims 21, 22, 24, 30-37, 39-50 and 52-58 have been canceled without prejudice. Applicants respectfully traverse this rejection with respect to the new claims, all of which depend from new claim 73.

As discussed above, the claims have been amended to recite a specific cell type (hematopoietic - e.g., CTL-EN cells), receptor type (GM-CSF/IL-3/IL-5) and cellular activity type (cell survival) in order to expedite prosecution of this application. The Examiner has repeatedly indicated that the "specification describes a method comprising hematopoietic cells, one particular subunit (the β_c chain shared by the GM-CSF/IL-3/IL-5 receptors) and the activity of cell survival" (Office Action dated December 20, 2005, p. 11, paragraph 1; *see also* Office Action dated May 17, 2005, paragraph overlapping pages 9-10). Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

Indefiniteness rejection

Claims 21, 22, 24, 30-37, 39-50 and 52-58 have been rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Claims 21, 22, 24, 30, 35-37, 43-50 and 52-58 have been canceled without prejudice. Applicants respectfully traverse this rejection with respect to the new claims, all of which depend from new claim 73.

In particular, the Examiner notes that residues 582-587 of the common ßc shown in Figure 1, and SEQ ID NO: 1, are KQASSF rather than HSRSLP.

Because SEQ ID NO: 1 contains a 16 amino acid leader (signal) sequence, the binding motif HSRSLP is at positions 598-603 instead of 582-587. The new claims reflect the proper amino acid position numbers of the claimed ^{598}HSRSLP^{603} binding motif. Applicants respectfully request withdrawal of this rejection.

Anticipation rejection

Claims 21, 22, 24, 30-37, 39-50 and 52-58 have been rejected under 35 U.S.C. § 102(b) as anticipated by Okuda et al., *Blood* 90(12):4759-4766 (1997) ("Okuda"). According to the Examiner, Okuda teaches a method of stimulating cell survival of Ba/F3 cells expressing GMFß-F8 mutant receptors. This method includes contacting the cells with GM-CSF. The Examiner contends that the instant application teaches that contacting cells expressing a ßc chain with GM-CSF stimulates phosphorylation of the binding motif containing Ser-585 and causes a 14-3-3 protein to bind this motif and stimulate cell survival. Thus, the Examiner argues that Okuda inherently anticipates the presently claimed invention.

Claims 21, 22, 24, 30, 35-37, 43-50 and 52-58 have been canceled without prejudice. Applicants respectfully traverse this rejection with respect to the new claims, all of which depend from new claim 73.

Applicants submit that Okuda does not teach or suggest all the claimed limitations of the amended claims either expressly or inherently. *Lewmar Marine v. Barient*, 827 F. 2d 744, 3, USPQ2d 1766 (Fed. Cir. 1987). In order for a characteristic to be inherent in a reference, it must be clear that "the missing descriptive matter is necessarily present in the reference and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Montsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

Okuda discloses a study which "evaluated the functions of the 8 tyrosine residues of the GMRß by using site-directed mutagenesis to either change all 8 tyrosines to phenylalanine residues (GMRß-F_8) or mutate 7 of the 8 tyrosines, leaving a single tyrosine residue intact" (Okuda, p. 4759, right col.). Okuda only discloses the positions of 3 of the 7 or 8 tyrosine mutations. The specific mutations disclosed by Okuda, Y577, Y612, and Y695, do not correspond to residues of ^{598}HSRSLP^{603} of the amino acid sequence now claimed. In fact, Okuda makes no reference to any amino acid residues of ^{598}HSRSLP^{603}, a sequence which does not contain any tyrosine or phenylalanine residues. Therefore, Okuda does not disclose or suggest mutating at least one of the residues of ^{598}HSRSLP^{603} as recited in the pending claims.

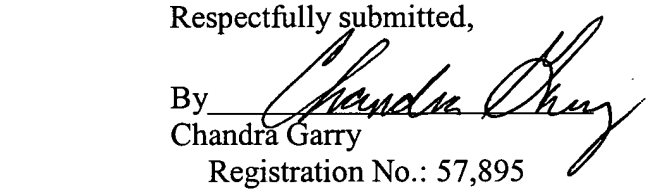
Accordingly, Okuda does not anticipate the presently claimed invention, and applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that the pending claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7601. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Dated: June 20, 2006

Respectfully submitted,

By 

Chandra Garry
Registration No.: 57,895
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicants